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(21) International Application Number: PCT/EP93/03269 (22) International Filing Date: 22 November 1993 (22.11.93) (30) Priority Data: 9225386.3 4 December 1992 (04.12.92) GB (71) Applicant (for all designated States except US): SMITHKLINE BEECHAM PLC [GB/GB]; New Horizons Court, Brentford, Middlesex TW8 9EP (GB). (72) Inventors; and (75) Inventors/Applicants (for US only): HAIGH, David [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). RAMI, Harshad, Kantilal [GB/GB]; SmithKline Beecham Pharmaceuticals, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB). (74) Agent: RUTTER, Keith; SmithKline Beecham, Corporate Intellectual Property, Great Burgh, Yew Tree Bottom Road, Epsom, Surrey KT18 5XQ (GB).		(81) Designated States: JP, US, European patent (AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE). Published With international search report.
(54) Title: HETEROCYCLIC DERIVATIVES AND THEIR USE IN PHARMACEUTICALS <div style="text-align: center; margin: 20px 0;"> $A^1 - X - (CH_2)_n - O - A^2 - CHR^1 - \overset{\overset{R^2}{ }}{\underset{\underset{R^4}{ }}{C}} - R^3 \quad (I)$ </div> (57) Abstract <p>A compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein: A¹ represents a substituted or unsubstituted aromatic heterocyclyl group; A² represents a benzene ring having three optional substituents; R¹ and R² each independently represents hydrogen or R¹ together with R² represents a bond; R³ and R⁴ each independently represents a nitrile group or a group of formula: -COR⁵ wherein R⁵ represents hydroxy, alkoxy, alkyl, aryl or a group of formula: -NR⁶R⁷ wherein R⁶ and R⁷ each independently represents hydrogen or alkyl or R⁶ and R⁷ together with the nitrogen atom to which they are attached form a heterocyclic ring; X represents NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; and n represents an integer in the range of from 2 to 6; a process for the preparation of such a compound, a pharmaceutical composition comprising such a compound and the use of such a compound and composition in medicine.</p>		

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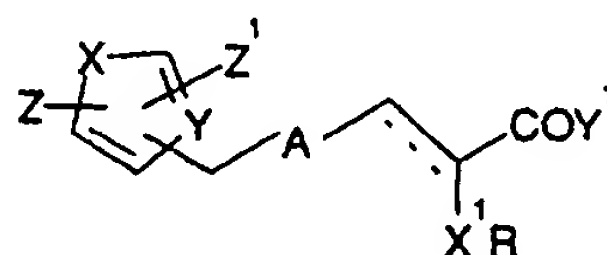
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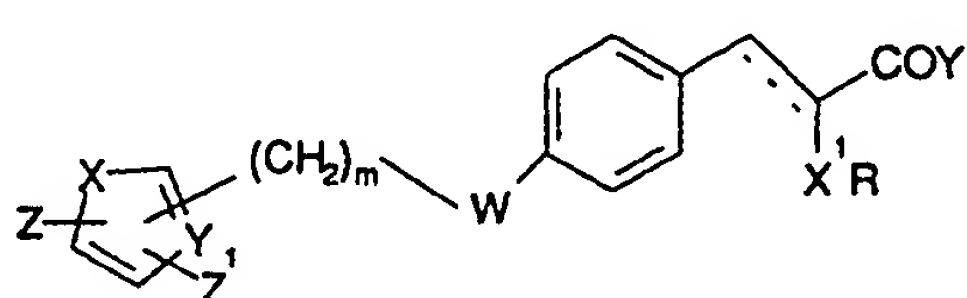
HETEROCYCLIC DERIVATIVES AND THEIR USE IN PHARMACEUTICALS

This invention relates to certain novel compounds, to a process for preparing such compounds, to pharmaceutical compositions containing such compounds and to the use of such compounds and compositions in medicine.

International Patent Application, Publication Number WO 91/19702 discloses compounds of formula (A) and (B):



10 and (A)

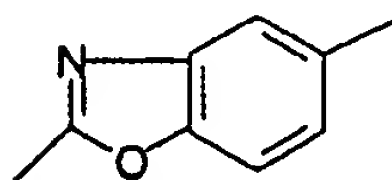


15 (B)
wherein A is



20

or



n is 0 or 1;

m is 0, 1 or 2;

25 ---- represents a bond or no bond;

R is (C₁-C₈)alkyl, (C₃-C₇)cycloalkyl, (C₃-C₈)alkenyl, (C₃-C₈)alkynyl, phenyl, (C₇-C₈)phenylalkyl, (C₂-C₈)alkanoyl, or one of said groups mono- or disubstituted with (C₁-C₃)alkyl, trifluoromethyl, hydroxy, (C₁-C₃)alkoxy, fluoro or chloro;

30 W is O, CO, CH₂, CHOH or -CH=CH-;

X is S, O, NR², -CH=CH-, -CH=N- or -N=CH-;

R² is hydrogen, (C₁-C₃)alkyl, phenyl or benzyl;

Y is CH or N;

Z is H, amino, (C₁-C₇)alkyl, (C₃-C₇)cycloalkyl, phenyl, or phenyl mono- or disubstituted with (C₁-C₃)alkyl, trifluoromethyl, (C₁-C₃)alkoxy, phenyl, phenoxy, benzyl, benzyloxy, fluoro or chloro;

Z¹ is hydrogen or (C₁-C₃)alkyl;

5 X¹ is O, S, SO or SO₂; and

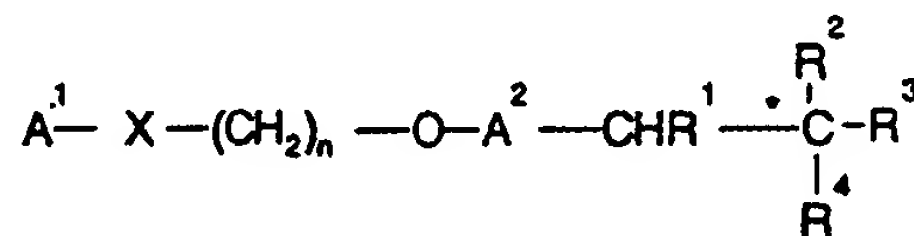
Y¹ is hydroxy, (C₁-C₃)alkoxy, phenoxy, benzyloxy, amino, (C₁-C₄)alkanoylamino, (C₁-C₄)alkanesulfonylamino, benzenesulfonylamino, naphthalenesulfonylamino, di[(C₁-C₃)alkyl]aminosulfonylamino, or one of said groups mono- or disubstituted with (C₁-C₃)alkyl, trifluoromethyl, hydroxy, (C₁-C₃)alkoxy, fluoro or chloro; the pharmaceutically-acceptable cationic salts thereof when Y¹ is hydroxy; and the pharmaceutically-acceptable acid addition salts thereof when the compounds contain a basic nitrogen atom.

The compounds of formula (A) are stated to be useful as hypoglycaemic and hypocholesterolaemic agents.

15 It has surprisingly been discovered that certain novel compounds show good blood-glucose lowering activity and are therefore of potential use in the treatment and/or prophylaxis of hyperglycaemia and are of particular use in the treatment of Type II diabetes.

These compounds are also indicated to be of potential use for the treatment and/or prophylaxis of other diseases including hyperlipidaemia and hypertension. They are also indicated to be of use in the treatment and/or prophylaxis of cardiovascular disease, especially atherosclerosis. In addition these compounds are considered to be useful for treating certain eating disorders, in particular the regulation of appetite and food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

Accordingly, the present invention provides a compound of formula (I):



30

(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

A¹ represents a substituted or unsubstituted aromatic heterocyclyl group;

35 A² represents a benzene ring having three optional substituents;

R¹ and R² each independently represents hydrogen or R¹ together with R² represents a bond;

R^3 and R^4 each independently represents a nitrile group or a group of formula $-COR^5$ wherein R^5 represents hydroxy, alkoxy, alkyl, aryl or a group of formula $-NR^6R^7$ wherein R^6 and R^7 each independently represents hydrogen or alkyl or R^6 and R^7 together with the nitrogen atom to which they are attached form a heterocyclic ring;

- 5 X represents NR wherein R represents a hydrogen atom, an alkyl group, an acyl group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted, or a substituted or unsubstituted aryl group; and
n represents an integer in the range of from 2 to 6.

- 10 Suitable aromatic heterocyclyl groups include substituted or unsubstituted, single or fused ring aromatic heterocyclyl groups comprising up to 4 hetero atoms in each ring selected from oxygen, sulphur or nitrogen.

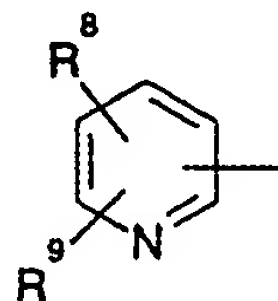
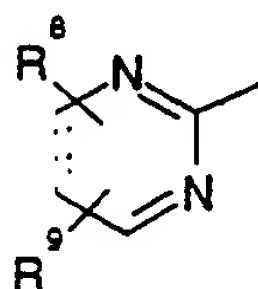
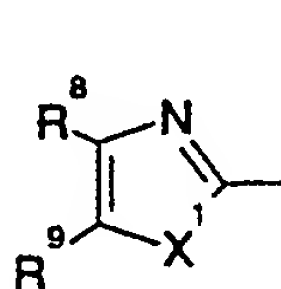
Favoured aromatic heterocyclyl groups include substituted or unsubstituted single ring aromatic heterocyclyl groups having 4 to 7 ring atoms, preferably 5 or 6 ring atoms.

- 15 In particular, the aromatic heterocyclyl group comprises 1, 2 or 3 heteroatoms, especially 1 or 2, selected from oxygen, sulphur or nitrogen.

Suitable values for A^1 when it represents a 5-membered aromatic heterocyclyl group include thiazolyl and oxazolyl, especially oxazolyl.

- 20 Suitable values for A^1 when it represents a 6-membered aromatic heterocyclyl group include pyridyl or pyrimidinyl, especially pyridyl.

Preferably, A^1 represents a moiety of formula (a), (b) or (c):



- 25 (a) (b) (c)

wherein:

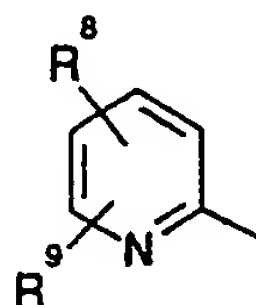
- 30 R^8 and R^9 each independently represents a hydrogen or halogen atom, an alkyl or alkoxy group or a substituted or unsubstituted aryl group or when R^8 and R^9 are each attached to adjacent carbon atoms, then R^8 and R^9 together with the carbon atoms to which they are attached may form a benzene ring wherein each carbon atom represented by R^8 and R^9 together is substituted or unsubstituted; and in the moiety of formula (a)

X^1 represents oxygen or sulphur.

- 35 Aptly, A^1 represents a moiety of the abovedefined formula (a).
Aptly, A^1 represents a moiety of the abovedefined formula (b).

Aptly, A¹ represents a moiety of the abovedefined formula (c).

A particular form of moiety (c) is a moiety (c'):

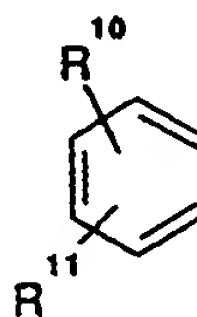


(c')

5

wherein R⁸ and R⁹ are as defined in relation to formula (c).

In one favoured aspect R⁸ and R⁹ together represent a moiety of formula (d):



(d)

10

wherein R¹⁰ and R¹¹ each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or substituted or unsubstituted alkoxy.

Suitably, R¹⁰ and R¹¹ each independently represent hydrogen, halogen, alkyl or alkoxy. Favourably, R¹⁰ represents hydrogen. Favourably, R¹¹ represents hydrogen. Preferably, R¹⁰ and R¹¹ both represent hydrogen.

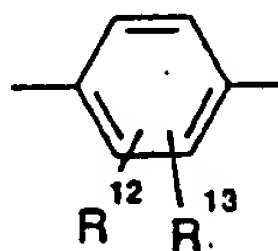
In a further favoured aspect R⁸ and R⁹ each independently represent hydrogen, alkyl or a substituted or unsubstituted phenyl group and more favourably, R⁸ and R⁹ each independently represent hydrogen, alkyl or phenyl.

Preferably, for the moiety of formula (a), R⁸ and R⁹ together represent the moiety of formula (d).

Preferably, for the moieties of formula (b), (c) or (c'), R⁸ and R⁹ both represent hydrogen.

Optional substituents for A² are selected from the group consisting of: halogen, substituted or unsubstituted alkyl and alkoxy.

Favourably, A² represents a moiety of formula (e):



(e)

wherein R¹² and R¹³ each independently represent hydrogen, halogen, substituted or

unsubstituted alkyl or alkoxy.

Suitably, R represents hydrogen or alkyl, especially alkyl.

When R is acyl, suitable acyl groups include alkylcarbonyl groups, for example acetyl.

5 Suitably, R^{12} and R^{13} each independently represent hydrogen, halogen, alkyl or alkoxy. Preferably, R^{12} and R^{13} each represent hydrogen.

Suitably, R^3 and R^4 each independently represents a group of formula $-COR^5$ wherein R^5 is as defined above.

Suitably, R^5 represents hydroxy or alkoxy.

10 When R^5 is alkyl, examples of R^5 include methyl.

When R^5 is aryl, examples of R^5 include phenyl.

An example of R^3 is CO_2CH_3 .

An example of R^4 is CO_2CH_3 .

When $-NR^6R^7$ represents a heterocyclic ring, favoured heterocyclic rings are
15 saturated or unsaturated, fused or monocyclic heterocyclic rings comprising 5, 6 or 7 ring atoms and optionally comprising 1 or 2 additional hetero-atoms, selected from O, S or N, in each ring. Favoured rings are saturated rings. Favoured rings are monocyclic rings. Favoured, additional hetero-atoms are N or O. Examples of such heterocyclic rings include N-pyrrolidinyl, N-piperidinyl and N-morpholinyl.

20 Favourably, n is 2.

As indicated above, a compound of formula (I), and the pharmaceutically acceptable salts thereof, may exist in one of several tautomeric forms, all of which are encompassed by the present invention as individual tautomeric forms or as mixtures thereof. The compounds of formula (I) may contain at least one chiral carbon, and
25 hence they may exist in one or more stereoisomeric forms. For example, when $R^1=R^2=H$ and $R^3 \neq R^4$, the carbon atom marked with an asterisk (*) in formula (I) is a chiral carbon. In addition, when R^1 together with R^2 represents a bond and $R^3 \neq R^4$, the compounds of formula (I) exist as geometric isomers. The present invention encompasses all of the stereoisomeric forms of the compounds of formula (I) and the
30 pharmaceutically acceptable salts thereof, whether as individual stereoisomers or as mixtures of isomers, including racemates.

Suitable substituents for any heterocyclyl group include up to 4 substituents selected from the group consisting of: alkyl, alkoxy, aryl and halogen or any two substituents on adjacent carbon atoms, together with the carbon atoms to which they
35 are attached, may form an aryl group, preferably a phenylene group, and wherein the carbon atoms of the aryl group represented by the said two substituents may themselves be substituted or unsubstituted.

When used herein, unless otherwise stated, the term 'aryl' includes phenyl and naphthyl; any aryl group mentioned herein may be optionally substituted with up to

wherein A^2 , R^1 and R^2 are as defined in relation to formula (I), $R^{3'}$ represents R^3 as defined in relation to formula (I) or a protected form thereof, $R^{4'}$ represents R^4 as defined in relation to formula (I) or a protected form thereof and R^a is a moiety convertible to a moiety of formula (f):

5



wherein A^1 , X and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f) and thereafter, if required, carrying out one or more of the following optional steps:

10

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) removing any necessary protecting group;
- (iii) preparing a pharmaceutically acceptable salt of the compound of formula (I)

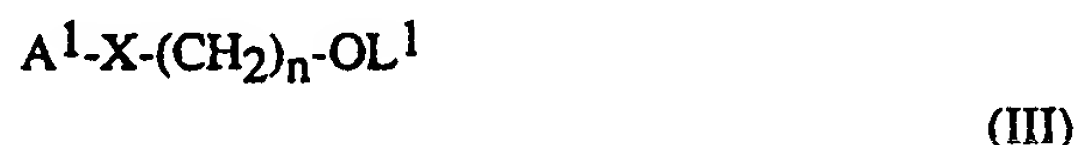
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and/or a pharmaceutically acceptable solvate thereof.

Preferably, R^a represents OH.

When R^a is OH, an appropriate reagent capable of converting R^a to the said moiety (f) is a compound of formula (III):

20



wherein A^1 , X and n are as defined in relation to formula (I) and L^1 represents a leaving group, such as a tosylate or mesylate group.

25

Preferably, when R^a is OH the compound of formula (II) is in an activated form.

A suitable activated form of a compound of formula (II) is an anionic form such as a salted form and especially an alkali metal salted form, for example a sodium salted form.

30

The activated form of the compound of formula (II) may be prepared using any appropriate method, thus when the activated form is a salted form the compound of formula (II) may be treated with an appropriate salting agent, for example an appropriate metal hydride base such as sodium hydride. The reaction between the compound of formula (II) and the salting agent may be carried out in any appropriate solvent such as an aprotic solvent for example dimethylformamide at any temperature providing a convenient rate of formation of the required product, such as a low to ambient temperature, for example a temperature in the range of from -10°C to 30°C , conveniently at 0°C .

35

The reaction between the compound of formula (II) and the appropriate

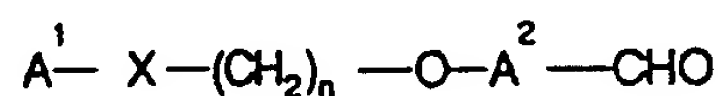
reagent capable of converting R^a to the said moiety (f) may be carried out under conditions suitable to the particular compound of formula (II) and the reagent chosen: For example the abovementioned reaction between the activated form of the compound of formula (II) wherein R^a represents OH, and the reagent of the
 5 abovedefined formula (III) may be carried out under conventional alkylation conditions, for example in an aprotic solvent, such as dimethylformamide, at any temperature providing a convenient rate of formation of the required product, such as an elevated temperature, for example in the range from 40°C to 120°C, for example at 80°C.

10 Favourably, the formation of the activated form of (II)- for example the formation of a salted form of (II) - may be carried out *in-situ* prior to the reaction of the activated form of (II) with the above defined compound of formula (III).

The compounds of formula (II) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for
 15 example those disclosed in Chemical Abstracts 101 (4) 31523f or Chem. Pharm. Bull., 1983, 31, 560.

The compounds of formula (III) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in EP0306228.

20 A compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, may also be prepared by reacting a compound of formula (IV):

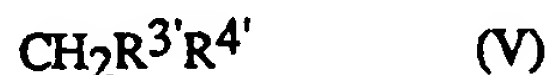


25

(IV)

wherein A^1 , A^2 , X and n are as defined in relation to formula (I) with a compound of formula (V):

30



wherein R^3 represents R^3 as defined in relation to formula (I) or a protected form thereof and R^4 represents R^4 as defined in relation to formula (I) or a protected form thereof; and thereafter if required carrying out one or more of the following optional
 35 steps:

(i) reducing a compound of formula (I) wherein R^1 and R^2 together represent a bond to provide a compound of formula (I) wherein R^1 and R^2 each represent hydrogen;

- (ii) converting a compound of formula (I) into a further compound of formula (I);
- (iii) remove any protecting group; and
- (iv) preparing a pharmaceutically acceptable salt of a compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

5 The reaction between the compounds of formulae (IV) and (V) may be carried out in a solvent such as toluene, suitably at an elevated temperature such as the reflux temperature of the solvent and preferably in the presence of a suitable catalyst such as piperidinium acetate or benzoate; favourably, the water produced in the reaction is removed from the reaction mixture, for example by means of a Dean and Stark
10 apparatus.

When R^3 or (R^4) in the required compound of formula (I) is COOH, then the corresponding group $R^{3'}$ (or $R^{4'}$) in the compound of formula (V) is usually in the form of a protected COOH group, suitably an ester, for example a C_{1-6} alkyl ester.

Generally, $R^{3'}$ is R^3 and $R^{4'}$ is R^4 .

15 The reduction of the compound of formula (I) wherein R^1 and R^2 together represent a bond may be carried out as described below.

The compounds of formula (IV) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in EP0306228.

20 The compounds of formula (V) are known compounds or they may be prepared using methods analogous to those used to prepare known compounds, for example those disclosed in Advanced Organic Chemistry, J. March, New York, Wiley.

25 The abovementioned conversion of a compound of formula (I) into a further compound of formula (I) includes:

- a) converting one group R into another group R;
- b) converting compounds wherein R^1 and R^2 together represent a bond into compounds wherein R^1 and R^2 each represent hydrogen; and
- c) conversion of one group R^3 into another group R^3 and/or conversion of one
30 group R^4 into another group R^4 .

The abovementioned conversions may as appropriate be carried out on any of the intermediate compounds mentioned herein.

The conversion of a compound of formula (I) to a further compound of formula (I) may be carried out by using any appropriate conventional procedure.

35 Suitable conversions of one group R into another group R include converting a group R which represents hydrogen into a group R which represents an acyl group; such conversion may be carried out using an appropriate conventional acylation procedure, for example treating an appropriately protected compound of formula (I) with an acylating agent. Thus acetic anhydride may be used to prepare the compound

of formula (I) wherein R is acetyl.

Above mentioned conversion (b) may be carried out using conventional hydrogenation methods, such as catalytic hydrogenation, or by dissolving metal reduction, for example using magnesium in methanol reduction as disclosed in
5 Tetrahedron Lett. 1986, 27, 2409.

Above mentioned conversion (c) may be carried out using the appropriate conventional procedure, for example when R³ and R⁴ each independently represent a group CO₂CH₃, they may each be converted to a group CO₂H by using lithium hydroxide in aqueous tetrahydrofuran or aqueous methanol.

10 It will be appreciated that in any of the abovementioned reactions including the abovementioned conversions (a), (b) and (c) any reactive group in the substrate molecule may be protected, according to conventional chemical practice.

Suitable protecting groups in any of the abovementioned reactions are those used conventionally in the art. Thus, for example, suitable hydroxyl protecting
15 groups include benzyl or trialkylsilyl groups.

The methods of formation and removal of such protecting groups are those conventional methods appropriate to the molecule being protected. Thus for example a benzyloxy group may be prepared by treatment of the appropriate compound with a benzyl halide, such as benzyl bromide, and thereafter, if required, the benzyl group
20 may be conveniently removed using catalytic hydrogenation or a mild ether cleavage reagent such as trimethylsilyl iodide or boron tribromide.

Where appropriate the isomeric forms of the compounds of formula (I) and the pharmaceutically acceptable salts thereof may be prepared as individual isomers using conventional chemical procedures.

25 As mentioned above the compounds of the invention are indicated as having useful therapeutic properties: The present invention accordingly provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use as an active therapeutic substance.

30 Thus the present invention provides a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia.

In a further aspect the present invention also provides a compound of formula
35 (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for use in the treatment and/or prophylaxis of hyperlipidaemia.

As indicated hereinbefore the present invention also provides a compound of formula (I) or a tautomeric form thereof and/or a pharmaceutically acceptable salt

thereof and/or a pharmaceutically acceptable solvate thereof for use in the treatment of hypertension, cardiovascular disease and certain eating disorders.

Cardiovascular disease includes in particular atherosclerosis.

Certain eating disorders include in particular the regulation of appetite and
5 food intake in subjects suffering from disorders associated with under-eating, such as anorexia nervosa, and disorders associated with over-eating, such as obesity and anorexia bulimia.

A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate
10 thereof, may be administered per se or, preferably, as a pharmaceutical composition also comprising a pharmaceutically acceptable carrier.

Accordingly, the present invention also provides a pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a pharmaceutically
15 acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

As used herein the term 'pharmaceutically acceptable' embraces compounds, compositions and ingredients for both human and veterinary use: for example the term 'pharmaceutically acceptable salt' embraces a veterinarily acceptable salt.

The composition may, if desired, be in the form of a pack accompanied by
20 written or printed instructions for use.

Usually the pharmaceutical compositions of the present invention will be adapted for oral administration, although compositions for administration by other routes, such as by injection and percutaneous absorption are also envisaged.

Particularly suitable compositions for oral administration are unit dosage
25 forms such as tablets and capsules. Other fixed unit dosage forms, such as powders presented in sachets, may also be used.

In accordance with conventional pharmaceutical practice the carrier may comprise a diluent, filler, disintegrant, wetting agent, lubricant, colourant, flavourant or other conventional adjuvant.

30 Typical carriers include, for example, microcrystalline cellulose, starch, sodium starch glycollate, polyvinylpyrrolidone, polyvinylpolypyrrolidone, magnesium stearate or sodium lauryl sulphate.

Most suitably the composition will be formulated in unit dose form. Such unit dose will normally contain an amount of the active ingredient in the range of from 0.1
35 to 1000 mg, more usually 0.1 to 500 mg, and more especially 0.1 to 250 mg.

The present invention further provides a method for the treatment and/or prophylaxis of hyperglycaemia in a human or non-human mammal which comprises administering an effective, non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof

and/or a pharmaceutically acceptable solvate thereof to a hyperglycaemic human or non-human mammal in need thereof.

The present invention further provides a method for the treatment of hyperlipidaemia in a human or non-human mammal, which comprises administering
5 an effective, non-toxic, amount of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, to a hyperlipidaemic human or non-human mammal in need thereof.

Conveniently, the active ingredient may be administered as a pharmaceutical
10 composition hereinbefore defined, and this forms a particular aspect of the present invention.

In the treatment and/or prophylaxis of hyperglycaemic humans, and/or the treatment and/or prophylaxis of hyperlipidaemic human, the compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt
15 thereof and/or a pharmaceutically acceptable solvate thereof, may be taken in doses, such as those described above, one to six times a day in a manner such that the total daily dose for a 70 kg adult will generally be in the range of from 0.1 to 6000 mg, and more usually about 1 to 1500 mg.

In the treatment and/or prophylaxis of hyperglycaemic non-human mammals,
20 especially dogs, the active ingredient may be administered by mouth, usually once or twice a day and in an amount in the range of from about 0.025 mg/kg to 25 mg/kg, for example 0.1 mg/kg to 20 mg/kg. Similar dosage regimens are suitable for the treatment and/or prophylaxis of hyperlipidaemia in non-human mammals.

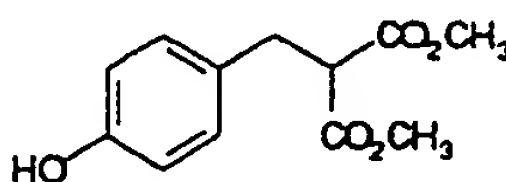
The dosages regimens for the treatment of hypertension, cardiovascular
25 disease and eating disorders will generally be those mentioned above in relation to hyperglycaemia.

In a further aspect the present invention provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a
30 medicament for the treatment and/or prophylaxis of hyperglycaemia.

The present invention also provides the use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperlipidaemia, hypertension, cardiovascular
35 disease or certain eating disorders.

No toxicological effects have been established for the compounds of formula (I) in the abovementioned dosage ranges.

The following Procedures and Examples illustrate the invention but do not limit it in any way.

Procedure 1**Dimethyl 2-(4-hydroxyphenylmethyl)propane-1,3-dioate**

5

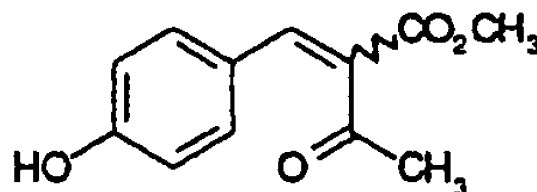
A solution of dimethyl 2-(4-hydroxyphenylmethylene)propane-1,3-dioate (*Chemical Abstracts* 101 (4), 31523f) (8.6 g) in methanol (250 mL) was hydrogenated over 10% Palladium charcoal (1.72 g) at room temperature and pressure for 5 hrs. The mixture was filtered and evaporated to afford the title compound, a gum, which was used without further purification.

¹H NMR δ (CDCl₃)
3.20 (2H, apparent d); 3.60 (1H,t); 3.73 (6H,s); 4.90 (1H, broad, exchanges with D₂O); 6.79 (2H,d); and 7.10 (2H,d).

15

Procedure 2**Methyl (E/Z)-2-acetyl-3-(4-hydroxyphenyl)propenoate**

20



A solution of 4-hydroxybenzaldehyde (10 g) and methyl acetoacetate (9.52 g) in toluene (150 mL) containing piperidine (0.25 mL) and acetic acid (0.25 mL) was heated at reflux for 2 hrs using a Dean and Stark apparatus. The reaction mixture was cooled and the solvent removed under reduced pressure to leave an oil. This was chromatographed on silica gel using 20 to 50% (gradient elution) ethyl acetate in hexane to afford a solid. Two crystallisations from acetone/hexane then furnished the title compound as a 4:1 mixture of geometric isomers (by ¹H NMR integration of the olefinic signals) and was used directly in the next stage.

30

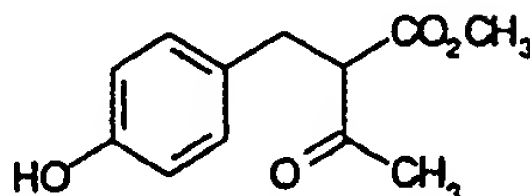
¹H NMR δ (CDCl₃)
2.41 (3H,s), 3.90 (3H,s), 6.93 (2H,d), 7.40 (2H,d); 7.50 (1H,br,exchanges with D₂O), 7.58 (0.8H*,s) and 7.68 (0.2H*,s).

35

The signals H* together constitute the olefinic proton resonance.

Procedure 3

Methyl 2-acetyl-3-(4-hydroxyphenyl)propanoate



5

A mixture of methyl (E/Z)-2-acetyl-3-(4-hydroxyphenyl)propanoate (2.67 g), methanol (30 mL), 10% Palladium on charcoal (0.20 g) and cyclohexene (5 mL) was heated at reflux for 2 hours and cooled. The catalyst was filtered off and the filtrate
10 evaporated to afford the title compound as an oil.

¹H NMR δ (CDCl₃)

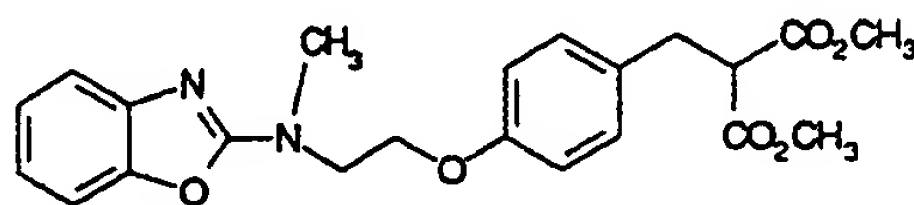
2.18 (3H,s), 3.09 (2H,d), 3.70 (3H,s), 3.77 (1H,t), 4.90 (1H,br, exchanges with D₂O), 6.72 (2H,d) and 7.01 (2H,d).

15

Example 1

Dimethyl 2-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenylmethyl]propane-1,3-dioate

20



Sodium hydride (60% dispersion in oil; 1.51 g) was added portionwise to an ice
25 cooled solution of dimethyl 2-(4-hydroxyphenylmethyl)propane-1,3-dioate (8.5 g) in dry N,N-dimethylformamide (100 mL) under a nitrogen atmosphere. The mixture was stirred at 0°C for 30 minutes prior to the addition of a solution of 2-[N-(2-benzoxazolyl)-N-methylamino]ethanol methanesulphonyl ester (*Eur. Patent Appl., Publication No.* 0306228) (9.64 g) in N,N-dimethylformamide (100 mL), and the
30 resulting mixture was then heated at 80°C for 22 hrs. The mixture was cooled, diluted with water (1.5 L), extracted with ethyl acetate (3 x 500 mL) and the combined ethyl acetate solutions were washed with water (4 x 1.5 L) and brine (1.5 L), dried (MgSO₄) and evaporated. The residual gum was chromatographed on silica gel with 1.5% methanol in dichloromethane as eluent to afford the title compound as
35 a gum.

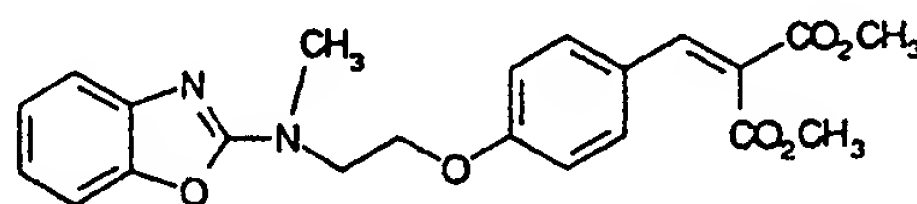
¹H NMR δ (CDCl₃)

3.15 (2H,d); 3.33 (3H,s); 3.61 (1H,t); 3.68 (6H,s); 3.92 (2H,t); 4.22 (2H,t); 6.78 (2H,d); and 7.00-7.40 (6H,complex).

5 Example 2

Dimethyl 2-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenylmethylene]propane-1,3-dioate

10



The title compound, a gum, was prepared from dimethyl 2-(4-hydroxyphenylmethylene)propane-1,3-dioate (*Chemical Abstracts*, **101** (4), 31523f) by a procedure similar to that described in Example 1.

15

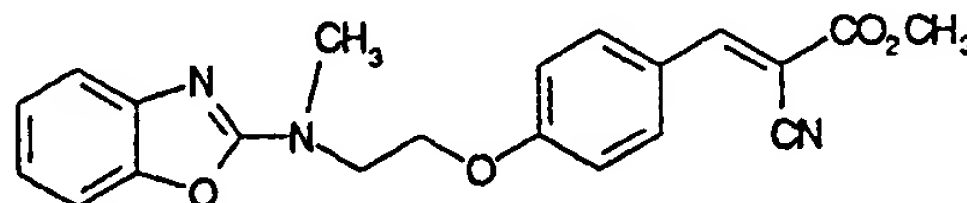
¹H NMR δ (CDCl₃)

3.40 (3H,s); 3.89 (3H,s); 3.92 (3H,s); 4.02 (2H,t); 4.35 (2H,t); 6.94 (2H,d); 7.09 (1H,t); 7.24 (1H,t); 7.34 (1H,d); 7.44 (3H,complex); and 7.76 (1H,s).

20 Example 3

Methyl (E)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]-ethoxy]phenyl]-2-cyanopropenoate

25



30

A mixture of 4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-benzaldehyde (*Eur. Patent Appl., Publication No. 0306228*) (2.96 g), methyl cyanoacetate (0.88 mL), piperidine (3 drops) and acetic acid (2 drops) dissolved in toluene (125 mL) was heated at reflux for 7 hrs. The mixture was cooled, evaporated and the residue crystallised from dichloromethane-hexane to afford the title compound, mp 128-30°C.

¹H NMR δ (CDCl₃)

35

3.35 (3H,s); 3.91 (3H,s); 3.98 (2H,t); 4.36 (2H,t); 6.90-7.05 (3H,complex); 7.17 (1H,t); 7.25 (1H,d); 7.35 (1H,d); 7.99 (2H,d); and 8.16 (1H,s).

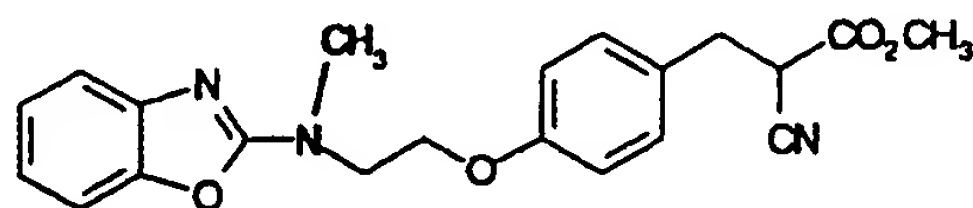
The geometry of the double bond was assigned unambiguously as E by long range

proton-carbon coupling constants (cf *J. Chem. Res.*, 1984, 311). The measured couplings 3J (H,CO₂Me)=6.7 Hz and 3J (H,CN)=13.8 Hz are consistent with literature values for the *E*-isomer.

5 Example 4

Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenyl]-2-cyanopropanoate

10



15

A solution of methyl (*E*)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-cyanopropenoate (1 g) in methanol (30 mL) was hydrogenated for 16 hrs over 10% Palladium on charcoal (0.20 g) at atmospheric pressure and ambient temperature. The catalyst was filtered off and the filtrate evaporated. The crude product was chromatographed on silica gel with 10 to 40% (gradient elution) ethyl acetate in hexane to afford the title compound as an oil.

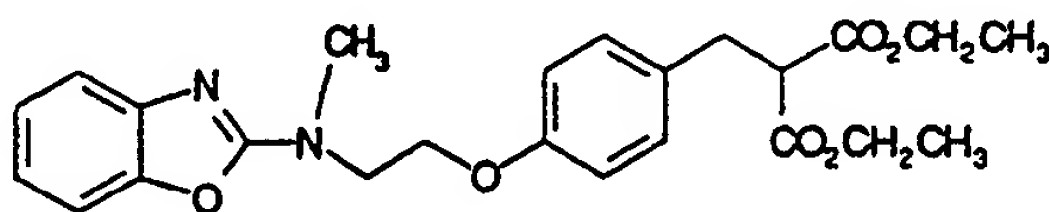
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¹H NMR δ (CDCl₃)

3.17 (2H,m), 3.35 (3H,s), 3.68 (1H,m), 3.78 (3H,s), 3.95 (2H,m), 4.25 (2H,m) and 6.83-7.37 (8H,m).

Example 5

Diethyl 2-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-benzyl]propane-1,3-dioate



The title compound, m.p. 71-72°C was prepared from diethyl 2-(4-hydroxyphenylmethyl)propane-1,3-dioate (*Chemical Abstracts*, 114, 121755f) and 2-[N-(2-benzoxazolyl)-N-methylamino]ethanol methanesulphonyl ester (*Eur. Patent Appl., Publication No.* 0306228) by a procedure similar to that described in Example 1.

35

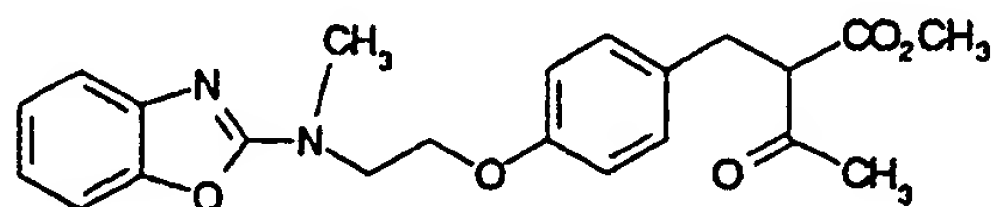
¹H NMR δ (CDCl₃)

1.20 (6H,t), 3.14 (2H,d), 3.34 (3H,s), 3.58 (1H,t), 3.93 (2H,t), 4.10-4.18 (6H,t), 6.79 (2H,d) and 7.00-7.37 (6H,m).

40

Example 6**Methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-acetylpropanoate**

5



The title compound was prepared from methyl 2-acetyl-3-(4-hydroxyphenyl)propanoate and 2-[N-(2-benzoxazolyl)-N-methylamino]ethanol methanesulphonyl ester (*Eur. Patent Appl., Publication No. 0306228*) by a procedure similar to that described in Example 1. The crude product was chromatographed on silica gel using 10 to 50% (gradient elution) ethyl acetate in hexane. Further chromatography on silica gel with 50 to 75% diethyl ether in hexane as eluent gave the title compound as an oil.

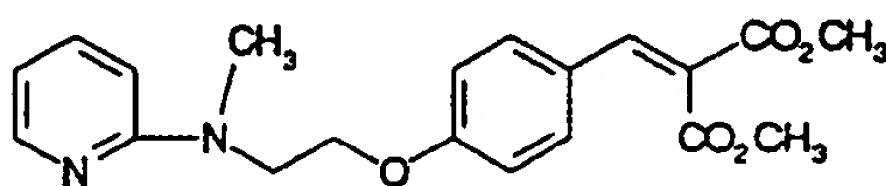
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¹H NMR δ (CDCl₃)

2.16 (3H,s), 3.08 (2H,d), 3.34 (3H,s), 3.68 (3H,s), 3.71 (1H,t), 3.93 (2H,m), 4.23 (2H,m), 6.78 (2H,d) and 7.00-7.37 (6H,m).

20 Example 7**Dimethyl 2-[4-[2-[N-(2-pyridyl)-N-methylamino]ethoxy]-benzylidene]propane-1,3-dioate**

25



A solution of 4-[2-[N-(2-pyridyl)-N-methylamino]ethoxy]benzaldehyde (1 g) (*Eur. Patent Appl. Publication No. 0306228*) and dimethyl malonate (0.52 g) in toluene (30 mL) containing piperidine (0.25 mL) and acetic acid (0.25 mL) was heated at reflux for 18 hrs using Dean and Stark apparatus. The solvent was removed under reduced pressure and the crude product was chromatographed on silica gel using 5 to 20% (gradient elution) acetone in hexane to afford the title compound as an oil.

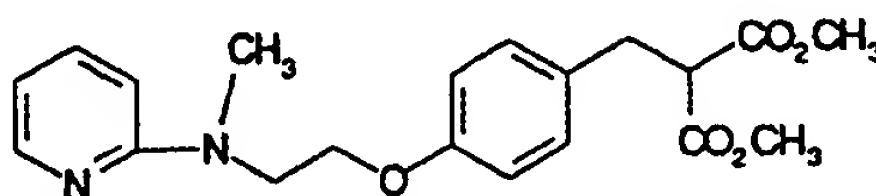
35 ¹H NMR δ (CDCl₃)

3.13 (3H,s), 3.83 (3H,s), 3.85 (3H,s), 3.99 (2H,t), 4.22 (2H,t), 6.51 (1H,d), 6.56 (1H,dd), 6.88 (2H,d), 7.36 (2H,d), 7.46 (1H,dd), 7.70 (1H,s) and 8.15 (1H,d).

Example 8

Dimethyl 2-[4-[2-[N-(2-pyridyl)-N-methylamin]ethoxy]-benzyl]propane-1,3-dioate

5



The title compound, an oil, was prepared from dimethyl 2-[4-[2-[N-(2-pyridyl)-N-methylamino]ethoxy]benzylidene]propane-1,3-dioate by a procedure similar to that described in Example 4.

10

¹H NMR δ (CDCl₃)

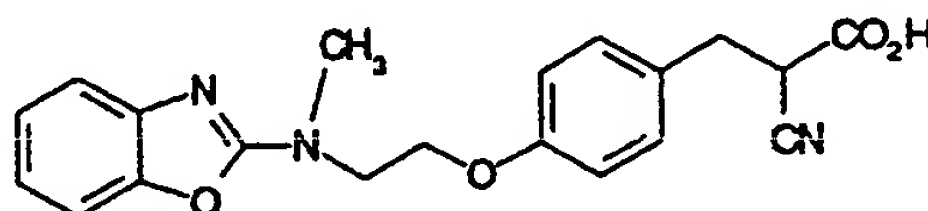
3.14 (3H,s), 3.15 (2H,d), 3.61 (1H,t), 3.69 (6H,s), 3.96 (2H,t), 4.14 (2H,t), 6.56 (2H,m), 6.80 (2H,d), 7.08 (2H,d), 7.44 (1H,dd) and 8.14 (1H,d).

15

Example 9

3-[4-[2-[N-(2-Benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-cyanopropanoic acid

20



A solution of methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-cyanopropanoate (439 mg) and lithium hydroxide monohydrate (155 mg) in a methanol:water mixture (1:1, 10 mL) was stirred at ambient temperature for two hours. The organic solvent was then removed under reduced pressure and the aqueous residue diluted with water (25 mL). This was acidified with dilute hydrochloric acid, extracted with ethyl acetate (3x20 mL) and the combined extracts were dried over magnesium sulphate. Filtration and subsequent removal of solvent afforded the product, m.p. 172-173°C.

30

¹H NMR δ (CDCl₃)

3.06 (2H,m), 3.23 (3H,s), 3.89 (2H,t), 4.25 (3H,m), 6.88-7.29 (8H,complex) and 13.5 (1H, br s; exchanges with D₂O).

35

DEMONSTRATION OF EFFICACY OF COMPOUNDS**Obese Mice, Oral Glucose Tolerance Test.**

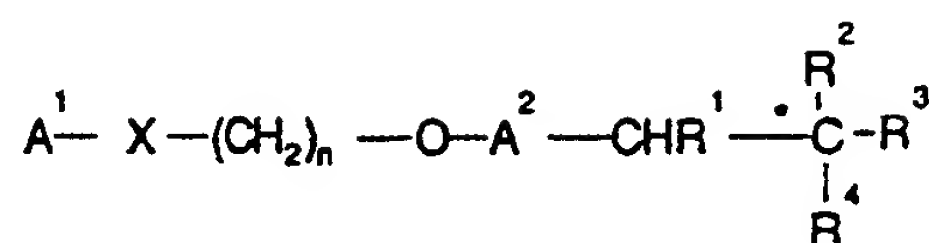
5 C57bl1/6 obese (ob/ob) mice were fed on powdered oxoid diet. After at least one week, the mice continued on a powdered oxoid diet or were fed powdered oxoid diet containing the test compound. After 8 days on the supplemented diet all of the mice were fasted for 5 hours prior to receiving an oral load of glucose (3g/kg). Blood samples for glucose analysis were taken 0,45,90 and 135 minutes after glucose administration and the results appear below as the percentage reduction in area under the blood glucose curve where test compound treated groups are compared with the control group. 8 mice were used for each treatment.

10

Example No.	Dose level in diet ($\mu\text{mol kg}^{-1}\text{diet}$)	% Reduction in area under blood glucose curve
1	1000	47
	30	44
2	1000	51
3	1000	46
	30	31
4	1000	57
	30	42
5	1000	54
	30	29
6	1000	52
8	100	27
9	1000	52
	30	36

Claims

1. A compound of formula (I):



5

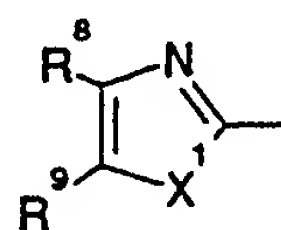
(I)

or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, wherein:

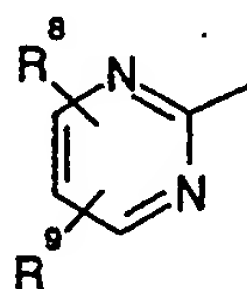
- 10 A^1 represents a substituted or unsubstituted aromatic heterocyclyl group;
 A^2 represents a benzene ring having three optional substituents;
 R^1 and R^2 each independently represents hydrogen or R^1 together with R^2 represents a bond;
 R^3 and R^4 each independently represents a nitrile group or a group of formula $-COR^5$
 15 wherein R^5 represents hydroxy, alkoxy, alkyl, aryl or a group of formula $-NR^6R^7$
 wherein R^6 and R^7 each independently represents hydrogen or alkyl or R^6 and R^7
 together with the nitrogen atom to which they are attached form a heterocyclic ring;
 X represents NR wherein R represents a hydrogen atom, an alkyl group, an acyl
 group, an aralkyl group wherein the aryl moiety may be substituted or unsubstituted,
 20 or a substituted or unsubstituted aryl group; and
 n represents an integer in the range of from 2 to 6.

2. A compound according to claim 1, wherein A^1 represents a moiety of formula (a), (b) or (c):

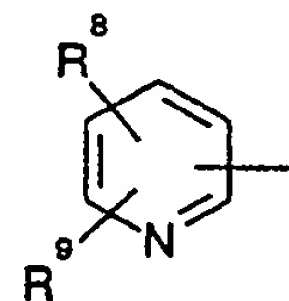
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(a)



(b)



(c)

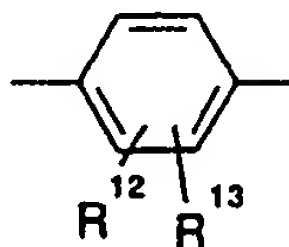
- 30 wherein:

R^8 and R^9 each independently represents a hydrogen or halogen atom, an alkyl or alkoxy group or a substituted or unsubstituted aryl group or when R^8 and R^9 are each attached to adjacent carbon atoms, then R^8 and R^9 together with the carbon atoms to which they are attached may form a benzene ring wherein each carbon atom

represented by R^8 and R^9 together is substituted or unsubstituted; and in the moiety of formula (a)

X^1 represents oxygen or sulphur.

- 5 3. A compound according to claim 1 or claim 2, wherein A^2 represents a moiety of formula (e):



- 10 wherein R^{12} and R^{13} each independently represent hydrogen, halogen, substituted or unsubstituted alkyl or alkoxy.

4. A compound according to any one of claims 1 to 3, wherein R^3 and R^4 each independently represents a group of formula $-COR^5$ wherein R^5 represents hydroxy, alkoxy, alkyl, aryl or a group of formula $-NR^6R^7$ wherein R^6 and R^7 each independently represents hydrogen or alkyl or R^6 and R^7 together with the nitrogen atom to which they are attached form a heterocyclic ring.
- 15

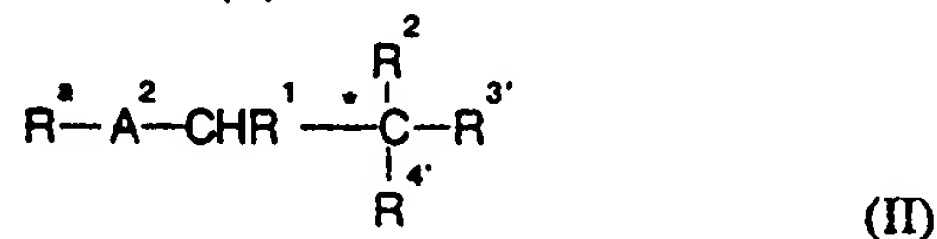
5. A compound according to any one of claims 1 to 4, wherein R^5 represents hydroxy or alkoxy.
- 20

6. A compound according to any one of claims 1 to 4, wherein R^5 represents hydroxy or alkoxy.

- 25 7. A compound according to any one of claims 1 to 5, wherein R^3 represents CO_2CH_3 and R^4 is CO_2CH_3 .

8. A process for the preparation of a compound of formula (I), or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or a pharmaceutically acceptable solvate thereof, which process comprises:
- 30

a) reacting a compound of formula (II):



wherein A^2 , R^1 and R^2 are as defined in relation to formula (I), $R^{3'}$ represents R^3 as defined in relation to formula (I) or a protected form thereof, $R^{4'}$ represents R^4 as defined in relation to formula (I) or a protected form thereof and R^a is a moiety convertible to a moiety of formula (f):

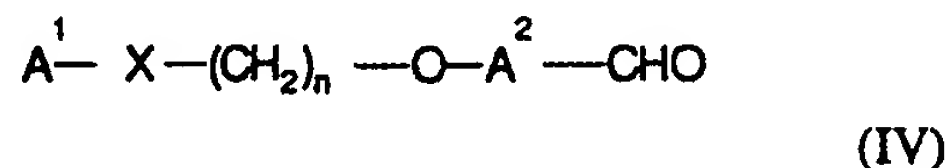
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wherein A^1 , X and n are as defined in relation to formula (I), with an appropriate reagent capable of converting R^a to the said moiety (f); or

10

b) by reacting a compound of formula (IV):



15

wherein A^1 , A^2 , X and n are as defined in relation to formula (I) with a compound of formula (V):



20

wherein $R^{3'}$ represents R^3 as defined in relation to formula (I) or a protected form thereof and $R^{4'}$ represents R^4 as defined in relation to formula (I) or a protected form thereof; and thereafter, if required, carrying out one or more of the following optional steps:

25

- (i) converting a compound of formula (I) to a further compound of formula (I);
- (ii) removing any necessary protecting group;
- (iii) preparing a pharmaceutically acceptable salt of the compound of formula (I) and/or a pharmaceutically acceptable solvate thereof.

30

9. A compound according to claim 1 selected from the list consisting of:

dimethyl 2-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenylmethyl]propane-1,3-dioate;

dimethyl 2-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-

35

phenylmethylene]propane-1,3-dioate;

methyl (E)-3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]-ethoxy]phenyl]-2-cyanopropenoate;

methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-phenyl]-2-

cyanopropanoate;

- diethyl 2-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]-benzyl]propane-1,3-dioate;
methyl 3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-acetylpropanoate;
5 dimethyl 2-[4-[2-[N-(2-pyridyl)-N-methylamino]ethoxy]-benzylidene]propane-1,3-dioate;
dimethyl 2-[4-[2-[N-(2-pyridyl)-N-methylamino]ethoxy]-benzyl]propane-1,3-dioate; ;
and
3-[4-[2-[N-(2-benzoxazolyl)-N-methylamino]ethoxy]phenyl]-2-cyanopropanoic acid;
10 or a tautomeric form thereof, and/or a pharmaceutically acceptable salt thereof, and/or
a pharmaceutically acceptable solvate thereof.

10. A pharmaceutical composition comprising a compound of the general formula (I), or a tautomeric form thereof, or a pharmaceutically acceptable salt thereof, or a
15 pharmaceutically acceptable solvate thereof, and a pharmaceutically acceptable carrier therefor.

11. A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate
20 thereof, for use as an active therapeutic substance.

12. A compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate
25 thereof, for use in the treatment of and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and certain eating disorders.

13. A method for the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease and eating disorders in a
human or non-human mammal which comprises administering an effective,
30 non-toxic, amount of a compound of the general formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate thereof to a human or non-human mammal in need thereof.

14. The use of a compound of formula (I), or a tautomeric form thereof and/or a pharmaceutically acceptable salt thereof and/or a pharmaceutically acceptable solvate
35 thereof, for the manufacture of a medicament for the treatment and/or prophylaxis of hyperglycaemia, hyperlipidaemia, hypertension, cardiovascular disease or certain eating disorders.

INTERNATIONAL SEARCH REPORT

Int. Application No

PCT/EP 93/03269

A. CLASSIFICATION OF SUBJECT MATTER

IPC 5 C07D263/58 C07D213/74 A61K31/42 A61K31/44 //C07D239/42

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 5 C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO,A,91 19702 (PFIZER INC.) 26 December 1991 cited in the application see claims 1,17,33-36 ----	1-4, 10-14
A	WO,A,92 02520 (BEECHAM GROUP PLC) 20 February 1992 see claims 1-4,14-16 ----	1-4, 10-14
A	CHEMICAL AND PHARMACEUTICAL BULLETIN. vol. 30, no. 10, October 1982, TOKYO JP pages 3580 - 3600 TAKASHI SOHDA ET AL 'Studies on antidiabetic agents.II. Synthesis of 5-[4- (1-methylcyclohexylmethoxy)-benzyl]thiazol idine-2,4-dione(ADD-3878) and its derivatives' see the whole document -----	1-4, 10-14

☐ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents :

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- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
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Date of the actual completion of the international search

2 March 1994

Date of mailing of the international search report

- 9. 03. 94

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Henry, J

INTERNATIONAL SEARCH REPORT

International application No.

PCT/EP 93/03269

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 13 is directed to a method of treatment of the human body, the search has been carried out and based on the alleged effects of the compounds.
2. ☐ Claims Nos.:
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
The definition of radical A1 as aromatic heterocyclic group is too broadly formulated to permit an adequate search. The search has essentially been limited to compounds of formula I which are supported by the examples.
Claims searched incompletely: 1
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/EP 93/03269

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO-A-9119702	26-12-91	US-A- 5089514	18-02-92
		AU-B- 646052	03-02-94
		AU-A- 7995691	07-01-92
		EP-A- 0533781	31-03-93

WO-A-9202520	20-02-92	AU-A- 8317891	02-03-92
		CA-A- 2093146	07-02-92
		EP-A- 0542816	26-05-93
		JP-T- 6500538	20-01-94
